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Abstract: PURPOSE: The aim of this quality control study was to assess the time to initial diagnostic procedures and the time to the first dose of antibiotics in patients with pneumococcal bacteremia, and to investigate whether the timeliness of these interventions influenced outcome. METHODS: We retrospectively studied patient characteristics, chronological sequence of diagnostic and therapeutic steps, and the course of disease of all patients with pneumococcal bacteremia at a Swiss university hospital between 2003 and 2009, and we analyzed associations between these factors and the length of hospital stay (LOS) and mortality. RESULTS: A total of 102 episodes of pneumococcal bacteremia in 98 patients were analyzed, of whom 15.7% died during hospitalization. The median time (interquartile range [IQR]) to the first antibiotic dose was 4.0 (2.0-5.9) h, and the median times (IQR]) to blood cultures, chest radiograph, lumbar puncture, and brain computed tomography (CT) scan or magnetic resonance imaging (MRI) were 1.4 (0.5-3.3), 2.5 (1.2-4.2), 4.2 (2.7-7.2), and 2.3 (0.6-6.2) h, respectively. The time to diagnostic procedures and therapy were not associated with LOS or death. Risk factors for death in the univariable analysis were: Charlson comorbidity index [odds ratio [OR] (95% confidence interval) per unit increase, 1.3 (1.1-1.6)], neutropenia [OR 10.1 (2.0-51.0)], human immunodeficiency virus (HIV) infection [OR 3.9 (1.1-13.8)], chronic respiratory disease [OR 4.4 (1.2-16.0)], chronic liver disease [OR 3.2 (1.0-9.7)], smoking [OR 3.8 (1.1-13.5)], injection drug use [OR 9.7 (1.5-63.7)], and antibiotic therapy within 6 months before admission [OR 4.0 (1.3-12.5)]. The multivariable analysis revealed age >60 years (P = 0.048) and alcoholism (P = 0.009) as risks for prolonged LOS. CONCLUSIONS: The outcome of pneumococcal bacteremia may be more influenced by patient characteristics than by minor differences in the timeliness of initial diagnostic and therapeutic measures within the first several hours after hospital admission.

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CLINICAL AND EPIDEMIOLOGICAL STUDY

Initial management of and outcome in patients with pneumococcal bacteremia: a retrospective study at a Swiss university hospital, 2003–2009

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Conclusions The outcome of pneumococcal bacteremia may be more influenced by patient characteristics than by minor differences in the timeliness of initial diagnostic and therapeutic measures within the first several hours after hospital admission.

Keywords *Streptococcus pneumoniae* · Bacteremia · Outcome · Sepsis · Treatment quality · Benchmark

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Introduction

Streptococcus pneumoniae infections are associated with severe morbidity and substantial mortality [1–5]. In numerous studies, different predictors influencing the outcome of pneumococcal bacteremia have been identified, including coronary heart disease, neutropenia, and

increasing age [1, 3, 5]. On the other hand, the morbidity of severe bacterial infections has been shown to be reduced with the prompt administration of appropriate antibiotic treatment [6–10]. Benchmarks for the timing of antibiotic therapy have been proposed for different organ system infections: treatment initiation within 4 h is considered to be appropriate for community-acquired pneumonia in people aged more than 65 years, and within 3 h for acute bacterial meningitis [11, 12]. Nevertheless, data on the association between the timeliness of initial diagnostic procedures or the initiation of therapy and outcome are scarce [13], and it is unknown whether specific benchmarks are applicable in the care of patients with pneumococcal bacteremia.

Within the antibiotic stewardship program at our hospital [14], we aimed to assess the quality of the initial management of patients with pneumococcal bacteremia, and to compare performance and outcomes with local and international guidelines and benchmarks [11, 12]. Therefore, we studied the associations between the variables "time to initiation of diagnostic procedures" (such as imaging, lumbar puncture, or blood culture collection), "time to initiation of antibiotic therapy", and in-hospital mortality and length of hospital stay (LOS).

Patients and methods

Ethics statement

Approval by the Research Ethics Board of the Canton of Zurich, Switzerland (address: Kantonale Ethikkommission Zürich, Sonneggstrasse 12, CH-8091 Zürich, Switzerland), was obtained. The ethics committee decided that patients' informed consent was not required because this study was a retrospective quality control project by infectious diseases physicians directly involved in patient care.

Patients and setting

We performed a retrospective study at the University Hospital Zurich, an 800-bed tertiary care teaching hospital that covers all specialties, except pediatrics and orthopedics. Six intensive care units offer a full range of clinical services in different departments of surgery and internal medicine.

The electronic database of the Institute of Medical Microbiology, University of Zurich, where all microbiological samples of the University Hospital Zurich are processed, was used to identify patients with the detection of *S. pneumoniae* in blood cultures. All patients with a community-acquired episode of pneumococcal bacteremia between January 1, 2003, and March 31, 2009, were eligible for inclusion in the study. An episode of pneumococcal bacteremia was determined by one or more blood culture pairs positive for *S. pneumoniae*. Isolates from an individual patient were considered to be a single episode if the interval between collections of the isolates was less than 30 days.

Bacteremia was not considered to be community-acquired if the patient was discharged from a hospital less than 7 days before the current hospital admission, if the first blood culture was obtained more than 1 week after hospital admission, or if the patient had no clinical signs and symptoms compatible with pneumococcal infection at the time of admission. We excluded patients who were referred from other hospitals, or who were transferred to another hospital or discharged before the end of treatment.

Data collection

Medical records were reviewed for the following information using a standardized data collection questionnaire: demographics (sex, age, residence prior to hospitalization [home vs. nursing home]), comorbidities (according to the Charlson comorbidity index [CCI]) [15] and the Chronic Disease Score (CDS) [16], neutropenia (defined as neutrophils $<0.5 \times 10^9$/L), cardiovascular diseases (such as coronary heart disease, history of myocardial infarction, congestive heart failure, or valvular heart disease), risk behavior (current alcoholism, smoking, injection drug use; as assessed by the admitting physician), prior antibiotic treatment, clinical presentation, initial management (imaging, lumbar puncture [if clinically indicated], blood cultures, and the initialization of antimicrobial therapy; all including the time period from the time of emergency room [ER] admission), laboratory parameters (hemoglobin, hematocrit, thrombocyte count, leucocyte count, blood urea nitrogen, serum creatinine, C-reactive protein, blood glucose, results from blood gas analysis), microbiology (susceptibility testing, serotyping), clinical course (systemic inflammatory response syndrome [SIRS; defined as two or more of the following: temperature (<36°C or >38°C); heart rate >90 beats per min; respiratory rate >20 breaths per min or $paCO_2 < 4.3$ kPa; leucocyte count <4,000/μL or >12,000/μL], sepsis (defined as one or more blood culture pairs positive), severe sepsis (defined as one or more blood culture pairs positive AND single organ failure), septic shock (defined as one or more blood culture pairs positive *AND* multiple organ failure *OR* need for catecholamines)), complications, and outcome (LOS, death). All times were calculated in relation to the moment of ER admission.

Microbiological analyses

Antimicrobial susceptibility testing for penicillin and ceftriaxone was performed according to the Clinical and

Laboratory Standards Institute (CLSI) recommendations at the Institute of Medical Microbiology, University of Zurich [17]. *S. pneumoniae* was identified using standard methodology, including colonial morphology on blood agar, bile solubility, and susceptibility to optochin. Additionally, all *S. pneumoniae* strains were then sent to the Swiss National Reference Center for Invasive Pneumococci (NRCP), where serotyping was carried out and susceptibility testing against levofloxacin, erythromycin, and cotrimoxazole was performed. Intermediate resistance was categorized as "not susceptible".

Data management and statistical analyses

Data were entered into the EpiData Data Entry, Data Management and Basic Statistical Analysis System 3.1 (EpiData Association, Odense, Denmark, 2008), and then cleaned and manually inspected for errors and outlying values, which were then confirmed or corrected with original records.

Differences in medians, for non-normally distributed data, were analyzed using the Wilcoxon rank-sum test, and differences in means, for normally distributed data, were assessed using Student's *t*-test. Differences in group proportions were assessed and univariable analyses for risk factors for death were performed using the Chi-square or Fisher's exact test, as appropriate. Multivariable analysis assessing the risk of death was not possible due to the small number of outcomes [18]. We used analysis of variance (ANOVA) to build multivariable models including predictors associated with LOS, treating LOS as a continuous variable.

All statistical analyses were performed using Stata 10.1 (StatCorp, College Station, TX, USA). A two-tailed test of significance with a *P*-value <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 141 blood cultures were tested positive for *S. pneumoniae* during the study period. Thirty-nine (27.7%) episodes did not meet the inclusion criteria [hospital-acquired infection: 10 (7.1%), transfer to another hospital before the end of treatment: 25 (17.7%), referral from another hospital: 8 (5.7%)]. Four (3.9%) patients had more than one episode of pneumococcal bacteremia, resulting in a total number of 102 episodes from 98 patients being available for analysis.

Table 1 summarizes the patient characteristics. The ratio of men to women was 1.4. The most common comorbidities were: chronic liver disease (23.5%), cardiovascular disease (20.6%), chronic renal disease (16.7%), human immunodeficiency virus (HIV) infection (13.7%), chronic respiratory disease (12.7%), and diabetes mellitus

Table 1 Characteristics of 98 patients (102 episodes) with pneumococcal bacteremia, 2003–2009

Variable	Result
Number of episodes of pneumococcal bacteremia	102 (100)
Male gender	59 (57.8)
Age, median (IQR)	59.2 (46.8–71.0)
≥60 years	47 (46.1)
Nursing home residence	7 (6.9)
Comorbidities	
Chronic disease score, median (IQR)	4 (1–5)
Charlson comorbidity index, median (IQR)	2 (1–4)
Impaired immunity	
Cellular immunodeficiency	
HIV infection	14 (13.7)
Immunosuppressive medication	9 (8.8)
Neutropenia	7 (6.9)
Hypo-/agammaglobulinemia	0 (0.0)
Splenectomy	4 (3.9)
Chronic disease of the respiratory tract	13 (12.7)
Cardiovascular disease	21 (20.6)
Diabetes mellitus	13 (12.7)
Chronic liver disease	24 (23.5)
Chronic renal disease	17 (16.7)
Concurrent medication	
Proton pump inhibitor therapy	20 (22.7)
Risk behavior	
Alcoholism	19 (18.6)
Smoking	38 (37.3)
Injection drug use	5 (4.9)
Prior antibiotic treatment	
For current episode	2 (2.0)
Within previous 6 months	21 (20.6)
Diagnosis at hospital admission	
Pneumonia	61 (59.8)
Other infection of the lower respiratory tract	6 (5.9)
Meningitis or cerebral abscess	10 (9.8)
Sinusitis	1 (1.0)
Otitis media	4 (3.9)
Sepsis	8 (7.8)
Fever without focus	10 (9.8)
Deterioration of general health condition	7 (6.9)
Suppurative arthritis	3 (2.9)
Disease of the gastrointestinal tract	2 (2.0)
Other	6 (5.9)

Numbers are *n* (%) unless otherwise specified

IQR interquartile range

(12.7%). Only in 35 cases (34.3%) was no risk behavior (none of alcoholism, smoking, or injection drug use) documented.

Patients presented with SIRS in 83 cases (81.3%). In 79 cases (77.5%), the bacteremia was classified as "sepsis", in three cases (3.7%) as "severe sepsis", and in 20 cases (19.6%) as "septic shock".

The most common diagnosis at discharge was pneumonia (73.5%), followed by meningitis (9.8%). The final diagnoses of otitis media (3.9%), sinusitis (2.9%), and sepsis without focus (1.0%) were less common. More than one diagnosis was made in 7.8% of cases; combinations were pneumonia and otitis media (3.9%), pneumonia and meningitis (2.0%), and pneumonia and arthritis (2.0%).

Outcome

The median [interquartile range (IQR)] LOS was 10 (4–17) days. In 31 (30.4%) cases, the patient had to be admitted to the intensive care unit (ICU), where the median LOS (IQR) was 4 (1–12) days. Sixteen (15.7%) of 98 patients died.

Table 2 Timing of the initial evaluation in 98 patients (102 episodes) with pneumococcal bacteremia

Diagnostic procedure	No. (%) of episodes with procedure	Time to procedure, median (IQR), h
Blood culture	102 (100)	1.4 (0.5–3.3)
Chest radiograph	97 (95.1)	2.5 (1.2–4.2)
Lumbar puncture	11 (10.8)	4.2 (2.7–7.2)
Brain CT scan or MRI	22 (21.6)	2.3 (0.6–6.2)

CT computed tomography, *MRI* magnetic resonance imaging

Antimicrobial susceptibility of pneumococcal isolates

Data regarding antimicrobial susceptibility could be obtained for 84 (82.4%) isolates. Of five strains (6.0%) with decreased susceptibility to penicillin, four were shown to have a minimum inhibitory concentration (MIC) of between 0.12 mg/L and 1 mg/L, and one had an MIC above 2 mg/L. All strains were susceptible to ceftriaxone. Fifteen (17.9%) strains were not susceptible to cotrimoxazole, eight (9.5%) strains were not susceptible to erythromycin, and one (1.2%) strain was not susceptible to levofloxacin.

Initial diagnostic procedures and time to antimicrobial administration

The times to initial diagnostic procedures are depicted in Table 2. The median time (IQR) to the first antibiotic dose was 4.0 (2.0–5.9) h (Fig. 1). In 100 (98.0%) of 102 episodes, the initial antibiotic treatment regimen corresponded to the local guidelines of the University Hospital Zurich. Empirically administered antibiotics did not have antimicrobial activity against *S. pneumoniae* in two (2.0%) episodes.

Risk factors for death

The following factors were associated with fatal outcome in the univariable analysis: Charlson comorbidity index [odds ratio (OR) (95% confidence interval) per unit increase, 1.3 (1.1–1.6)], neutropenia [OR, 10.1 (2.0–51.0)], HIV infection [OR 3.9 (1.1–13.8), chronic respiratory disease (OR 4.4 (1.2–16.0)], chronic liver disease [OR 3.2

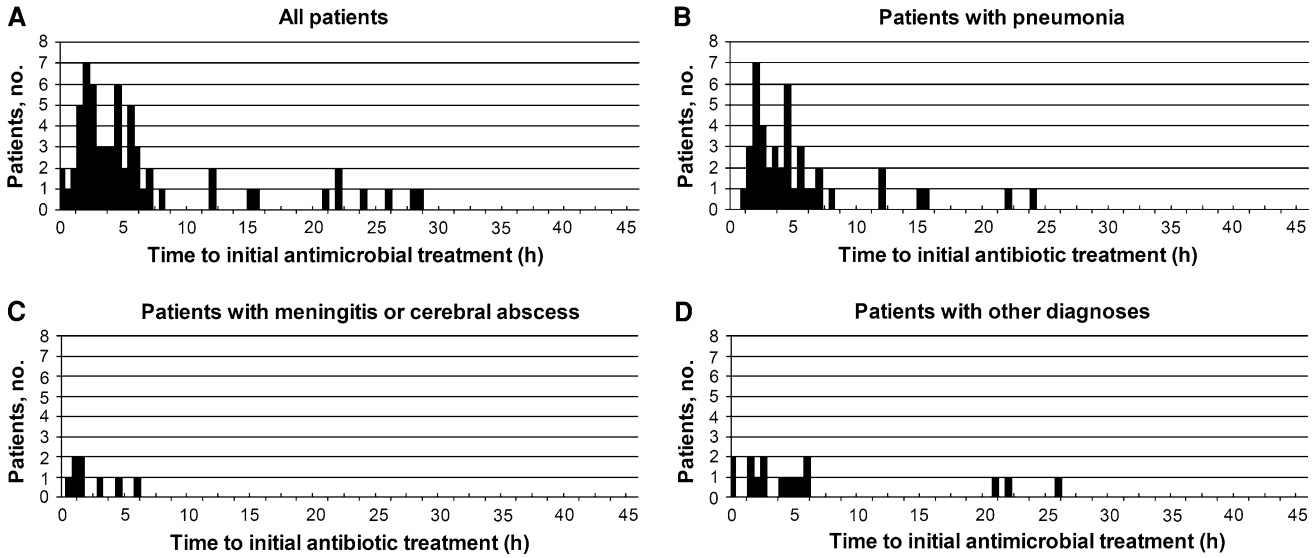

Fig. 1 The time to initial antimicrobial treatment in patients with pneumococcal bacteremia and different initial diagnoses

(1.0–9.7)], smoking [OR 3.8 (1.1–13.5)], injection drug use [OR 9.7 (1.5–63.7)], and antibiotic therapy within the previous 6 months before admission [OR 4.0 (1.3–12.5)] (Table 3). There was no association between fatal outcome and antimicrobial susceptibility rates (data not shown).

Overall, no association was found between the rapid initiation of diagnostic steps and survival: the median time (IQR) to blood culture (survivors: 1.3 (0.5–3.2) h vs. deceased: 1.8 (1.2–5.5) h, $P = 0.20$), the median time (IQR) to chest radiograph (survivors: 2.4 (1.2–4.0) h vs. deceased: 2.8 (1.4–7.2) h, $P = 0.59$), and the median time (IQR) to brain computed tomography (CT) scan or magnetic resonance imaging (MRI) (survivors: 1.65 (0.6–4.3) h vs. deceased: 13.0 (5.0–116.6) h, $P = 0.13$) were not different between survivors and deceased patients. Compared to other initial diagnoses, the time to blood cultures was decreased if patients were admitted with "pneumonia" (median time (IQR): 1.2 (0.5–2.7) h; $P < 0.001$) or "meningitis or cerebral abscess" (median time (IQR): 0.8 (0.3–1.2) h; $P = 0.016$).

Deceased patients received their first dose of antibiotics after a median time (IQR) of 3.3 (1.8–4.3) h, compared to 4.2 (2.0–5.9) h in survivors ($P = 0.56$) (Fig. 2). The initial diagnosis did not affect the time to the first antibiotic dose and there was no association between survival and the rapid administration of initial antibiotic therapy; the case fatality rate was 21.9% (7 of 32 episodes) if antibiotics were administered within 4 h of ER admission and 12.5%

Table 3 Risk factors for death in 98 patients (102 episodes) with pneumococcal bacteremia

Characteristic	Survivors ($n = 86$)	Deceased ($n = 16$)	OR (95% CI)	P-value
Male gender	48 (55.8)	11 (68.8)	1.74 (0.56–5.44)	0.34
Age >60 years	40 (46.5)	7 (43.8)	0.89 (0.31–2.62)	0.90
Admitted from nursing home	4 (4.7)	3 (18.8)	4.73 (0.95–23.06)	0.06
Chronic disease score, median (IQR)	4 (2–5)	2 (0–5)		0.37
Charlson comorbidity index, median (IQR)	2 (1–3)	3 (2–7)		0.013
Co-morbidities				
HIV infection	9 (10.5)	5 (31.3)	3.89 (1.10–13.75)	0.035
Immunosuppressive medication	8 (9.3)	1 (6.3)	0.58 (0.07–5.02)	0.62
Neutropenia	3 (3.5)	4 (25.0)	10.06 (1.98–51.02)	0.005
Splenectomy	4 (4.7)	0 (0.0)	–	1.00
Chronic disease of the respiratory tract	8 (9.3)	5 (31.3)	4.43 (1.23–15.99)	0.023
Cardiovascular disease	19 (22.1)	2 (12.5)	0.50 (0.11–2.41)	0.39
Diabetes mellitus	11 (12.8)	2 (12.5)	0.97 (0.19–4.88)	0.97
Chronic liver disease	17 (19.8)	7 (43.8)	3.16 (1.03–9.69)	0.044
Chronic renal disease	15 (17.4)	2 (12.5)	0.68 (0.14–3.30)	0.63
Malignancy	3 (3.5)	2 (12.5)	3.95 (0.61–25.82)	0.15
Proton pump inhibitor therapy	16 (21.9)	4 (26.7)	1.30 (0.36–4.62)	0.69
Alcoholism	14 (16.3)	5 (31.3)	2.34 (0.70–7.78)	0.17
Smoking	29 (33.7)	9 (56.3)	3.80 (1.07–13.46)	0.038
Injection drug use	2 (2.3)	3 (18.8)	9.69 (1.48–63.65)	0.018
Antibiotic pretreatment for current episode	2 (2.3)	0 (0.0)	–	1.00
Antibiotic therapy within previous 6 months	14 (16.3)	7 (43.8)	4.00 (1.27–12.53)	0.020
Initial diagnosis at the time of hospital admission				
Infection of the respiratory tract	59 (68.6)	8 (50.0)	0.46 (0.16–1.35)	0.16
Meningitis or other CNS infection	7 (8.1)	3 (18.8)	2.60 (0.60–11.38)	0.20
Sinusitis or otitis media	4 (4.7)	1 (6.3)	1.37 (0.14–13.09)	0.79
Sepsis or fever without focus	13 (15.1)	3 (18.8)	2.27 (0.73–7.07)	0.16
SIRS	71 (82.6)	12 (75)	0.63 (0.18–2.24)	0.48
Inadequate empiric antibiotic therapy	2 (2.4)	0 (0.0)	–	1.00
Delay of antibiotic therapy >4 h	31 (36.0)	6 (37.5)	0.51 (0.13–1.95)	0.33
Delay of antibiotic therapy >8 h	14 (16.3)	5 (31.3)	1.09 (0.20–5.90)	0.92

Numbers are *n* (%) unless otherwise specified

OR odds ratio, *CI* confidence interval, *IQR* interquartile range, *CNS* central nervous system

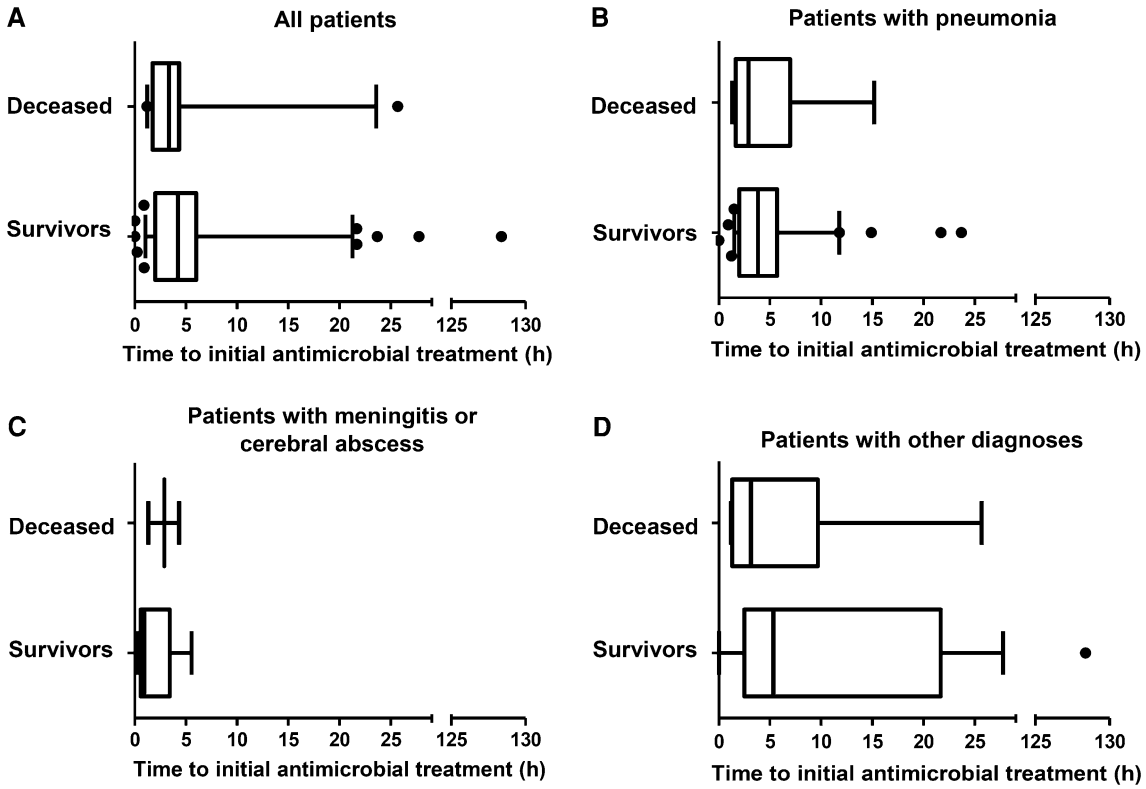

Fig. 2 Association between the time to the initial antibiotic treatment and fatal outcome in patients with pneumococcal bacteremia and different initial diagnoses

(4 of 32 episodes) in patients who received their first antibiotic dose more than 4 h after hospital admission ($P = 0.32$).

Length of hospital stay

The following variables among those assessed as risk factors for death (Table 3) were found to be associated with an increase in the LOS among survivors: age >60 years (median LOS (IQR) in patients aged >60 years: 11.5 (8.5–25.5) days vs. 6.0 (2.0–15.0) days in those aged ≤60 years, $P = 0.006$), alcoholism (median LOS (IQR) in patients reporting current alcoholism: 19.0 (13.0–30.0) days vs. 9.0 (4.0–15.0) days in those not abusing alcohol, $P = 0.003$), and admission diagnosis of "sepsis" (median LOS (IQR) in patients admitted with "sepsis": 15.5 (9.0–29.0) days vs. 9.5 (4.0–15.5) days in those admitted with other diagnoses, $P = 0.028$). There was no association between the LOS and time to blood culture, time to first antibiotic dose, time to imaging (chest radiograph or brain CT/MRI), and time to lumbar puncture.

Multivariable analysis revealed age >60 years ($P = 0.048$) and alcoholism ($P = 0.009$) as independent predictors for an increase in the LOS.

Discussion

In this retrospective study of pneumococcal bacteremia in a Swiss university hospital over a 6-year period, we were unable to demonstrate an association between initial patient management and fatal outcome and LOS, respectively. Initial diagnostic steps and antimicrobial therapy were not delayed in deceased patients, and 98% of patients received an initial antimicrobial therapy that was adequate for pneumococcal bacteremia according to local and international guidelines. Factors associated with fatal outcome in the univariable analysis were increasing comorbidity scores, neutropenia, HIV infection, chronic respiratory disease, chronic liver disease, smoking, injection drug use, and previous antibiotic therapy in the past 6 months. Factors independently associated with prolonged LOS were age >60 years and alcoholism.

We were unable to find other studies that assessed the association between early diagnostic and therapeutic management and survival in pneumococcal bacteremia. Several studies have demonstrated that the earlier administration of antibiotics reduces mortality in community-acquired pneumonia [6–8, 13]. There are, however, other data indicating that the early administration of antibiotics

does not necessarily lead to better survival [19]. Similar to our results, Cheng and Buising [19] observed that deceased patients with community-acquired pneumonia received their first dose of antibiotics after a median of 1.5 h, in contrast to survivors who received their first dose of antibiotics after a median of 2.9 h. The authors hypothesized that this finding may be due to either a true lack of association, in that minor differences in antibiotic administration within the first 8 h do not affect mortality, or to confounding by severity because patients at the highest risk of death were found to have received antibiotics earlier. Overall, limitations of the available data result in a continuing debate over the mandate to deliver antibiotics within 4 h of arrival for patients being admitted to the hospital with community-acquired pneumonia [20]. With regards to our study, pneumococcal bacteremia is most often secondary to infections of various organ systems that differ in severity. Thereby, an advantage of survival would be expected predominantly in those individuals who were more severely ill, such as patients with CNS infection [21], whereas the outcome of infections that develop over a longer period of time may not be affected by differences in the initiation of antimicrobial therapy, if this occurs within a few hours [8].

Even though the median time to the first dose of antibiotics for pneumonia and meningitis observed in our study met the proposed time limits from earlier publications [11, 12], it has to be noted that a significant number of patients received delayed initial antibiotic treatment in our dataset. This may result from the wide range of possible presentations of these patients, rendering initial diagnostic and therapeutic choices difficult. Clinical deterioration may be delayed especially in otherwise healthy subjects, possibly explaining the fact that patients at a higher risk for death tend to receive diagnostic and therapeutic steps in a more timely manner. Nevertheless, the overall case fatality rate of 15.7% in our study is below average as compared to other published data, which may be indicative of adequate treatment quality given the case mix that is usually seen in an academic center [1–5].

Our study has several limitations. First, the generalizability of our findings may be limited in that we present results from a retrospective study of pneumococcal bacteremia conducted in a single university hospital in Switzerland. The results may be different in other geographic areas and in non-academic centers. Second, our study is limited by the lack of power, in that only 16 deceased patients were detected in a 6-year study period. We were, thus, unable to perform multivariable analysis assessing confounders of the possible association between timely initial management and fatal outcome. Selection bias might have crept in by excluding patients who were transferred to another hospital or discharged before the end of treatment. Patients treated over the entire course of disease at an academic center likely have different characteristics from those discharged on oral antibiotics or transferred to secondary or tertiary hospitals for the completion of treatment. The variability of the duration of infection prior to presentation in the hospital is an additional confounding factor, which inherently renders the interpretation of the findings regarding the interval between hospital presentation and diagnostic and therapeutic measures difficult. Last, the range of conditions varied between the infection of cryptic origin to meningitis, and the impact of delayed antibiotic administration in some of these conditions may be less significant than others. On the other hand, the existing literature suggests that pneumococcal bacteremia, per se, is a strong indicator of a serious clinical condition, irrespective of the origin, and, thus, the variations in clinical conditions may be of less importance [22].

The findings of this study confirm that pneumococcal bacteremia is a disease with significant morbidity and mortality requiring a timely and adequate initial management. Our results indicate that there is a need for further investigation to help identify patients presenting with atypical clinical symptoms who may be at risk for delayed initial diagnostic and therapeutic management. Larger scale studies are needed in order to draw appropriate conclusions about a mandate to deliver antibiotics within a certain window of time after hospital admission in pneumococcal bacteremia, and, particularly, to characterize populations for which the adherence to such benchmarks improves patient outcomes.

It has to be kept in mind that benchmarks do not necessarily result in improved overall patient care because care providers might focus too much on easily measurable outcome data while neglecting other important challenges. In the field of infectious diseases, an excessively broad and thoughtless application of guidelines may have particularly negative consequences and, at worst, may lead to an increase in adverse events or bacterial resistance rates through an untimely and unnecessary use of antibiotics in viral or other non-bacterial inflammatory diseases [23]. A study on the 4-h antibiotic administration rule, without showing any reduction of mortality, revealed that strict use of this benchmark resulted in the misdiagnosis of pneumonia in almost 20% of patients and, consecutively, to the inappropriate use of antimicrobials [24, 25].

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Conflict of interest The authors have declared that no conflict of interest exists.

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